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Comparisons of telomere lengths in peripheral blood and cerebellum in Alzheimer's disease

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Abstract

Background: Alzheimer's disease (AD) patients have been reported to have shorter telomeres in peripheral blood leukocytes (PBLs) than age-matched control subjects. However, it is unclear if PBL telomere length reflects brain telomere length, which might play a more direct role in AD pathogenesis. We examined the correlation between PBL and cerebellum telomere length in AD patients, and compared telomere lengths in cerebella from individuals with AD versus age-matched control subjects.
Methods: Mean telomere lengths were measured using quantitative telomere polymerase chain reaction of genomic DNA prepared from matched PBL and cerebellum samples from 29 individuals with pathologically confirmed sporadic AD. Telomere length was also measured in cerebellum samples of 30 AD patients versus 22 unaffected age-matched control subjects.
Results: The PBL and cerebellum telomere lengths were directly correlated in individuals with AD ($r = 0.42$, $P = 0.023$). Nonetheless, cerebellum telomere lengths were not significantly different in AD patients and age-matched control subjects.
Conclusions: Reduced PBL telomere length in AD might not reflect reduced telomere length in bulk brain tissue, but may be a marker of changes in a subset of brain tissues or other tissues that affect the pathogenesis of AD.

Keywords: Alzheimer's disease; Telomere; Cerebellum; Aging

1. Introduction

Alzheimer's disease (AD) is the major cause of dementia in the elderly, and affects more than 40% of individuals over the age of 85 [1]. The accumulation of fibrillary proteins, including the Aβ peptide in senile plaques and tau protein in neurofibrillary tangles, appears to be central to the pathogenesis of AD [2–4]. It is nonetheless unclear why individuals with the predominant, sporadic form of AD are more prone to disease, although some genetic risk factors were identified [5,6]. Further, it is unclear why age is the major risk factor for AD; possibilities include age-related inflammatory, oxidative, and immune changes, and a time-dependent accumulation of misfolded proteins. Telomere shortening, a known age-related chromosomal change that occurs in most human tissues [7–9], emerged recently as a potential contributor to the pathogenesis of AD.

Telomeres are repeated sequences and associated proteins that protect, or ''cap,'' the ends of chromosomes [10]. The ''uncapping'' of telomeres leads to the degradation and fusion of chromosome ends, and to either permanent cell-cycle arrest (''cell senescence'') or death via apoptosis. Telomere length is important for capping [11]. Because the DNA-replication machinery is incapable of fully replicating the ends of linear molecules, and also because of nucleolytic degradation and oxidative DNA damage, telomeres shorten as

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cells divide. Some cells express high levels of the enzyme telomerase, which adds telomere repeats to existing telomere ends and thus counteracts shortening. However, there is insufficient telomerase in most human cells to prevent telomere shortening. It is clear that telomeres shorten with age in many human tissues, including skin, kidney, liver, blood vessels and peripheral white blood cells [7].

Telomere shortening limits the replicative lifespan of many different human cells in culture, and evidence is accumulating that telomeres become critically short in aging human tissues, and thus contribute to age-associated pathology. For example, individuals over age 60 years who have telomeres in the bottom half of the length distribution have 1.9-fold higher mortality rates than age-matched individuals with telomeres in the top half of the length distribution ($P = 0.004$) [12]. Further, individuals with dyskeratosis congenita, who have a 50% decrease in telomerase activity, suffer from several age-associated pathologies (e.g., bone marrow failure and osteoporosis) [13], and telomere defects may contribute centrally to the pathogenesis of the Werner premature aging syndrome [14–16]. An exponential increase with age in the frequency of uncapped telomeres and the heterochromatinization of the nuclear genome in the skin of nonhuman primates indicates an association between age-related telomere dysfunction and cellular senescence in vivo [17]. Further, telomere length may be a heritable factor correlated with lifespan [18]. Mean telomere length in a given tissue or cell type varies among individuals of the same age [19–21], and individuals born with a greater telomere reserve might be protected from the effects of age-related telomere attrition.

Although telomeres will shorten with cell division, some dividing cells express telomerase (e.g., activated lymphocytes and progenitor cells of epithelial and hematopoietic tissues), which can slow or even reverse telomere shortening. Thus in older individuals, the telomere lengths of tissues with abundant dividing cells may have a complicated relationship with inherited telomere lengths. On the other hand, the low levels of cell turnover and lack of significant telomerase in normal brains yield slow and regular age-related telomere shortening that may allow telomere length at a given age to have a simpler relationship with inherited telomere lengths. Indeed, cerebral cortex telomere lengths were found to shorten with age in a cross-sectional study of individuals up to 70–79 years of age, but were then directly correlated with age in individuals aged 80 years and older [22]. This was interpreted as a survivor effect, where individuals who had inherited longer telomeres had a greater likelihood of living to an older age.

Four studies have connected telomere length to AD, despite the lack of an apparent association in one early, small study [23]. The first study found that individuals with AD had shorter telomere lengths in peripheral blood mononuclear cells than did age-matched control subjects [24]. Further, T-cell telomere length was correlated with Mini-Mental State Examination score, and inversely correlated with serum levels of the proinflammatory cytokine tumor necrosis factor-α, suggesting that short telomeres might induce immune dysfunction and thus contribute to the pathogenesis of AD. The second study examined women with Down syndrome, and found shorter telomeres in T cells of individuals with AD-type dementia than in age-matched control subjects [25]. The third, a case control study of 257 individuals, found reduced peripheral blood leukocyte (PBL) telomere length in AD patients compared with control subjects [26]. Moreover, among individuals with AD, short telomeres were associated with higher mortality rates. A fourth study confirmed the association between short PBL telomere length and AD, and was the first to examine brain (hippocampus) telomere length in histopathologically validated AD patients [27]. Surprisingly, telomere lengths in the hippocampus were found to be 49% longer in AD patients than in control subjects ($P < 0.01$). However, because glial cells can upregulate telomerase and lengthen their telomeres upon proliferating in response to injury [28–30], the gliosis known to be associated with the most active sites of AD pathology, such as the hippocampus, likely contributed to the increased overall telomere length of cells observed in this brain region. Together, these four studies indicate that telomere length in peripheral blood cells is a marker of AD, although many questions remain about the relationship and significance of PBL telomere length to the pathogenesis of AD.

Here we examined the association between PBL and cerebellum telomere lengths in AD, and also compared telomere lengths in the cerebella of AD patients and control subjects. We chose the cerebellum because whereas it may suffer limited pathology in AD, including atrophy of the molecular and granular layers [31], it does not experience gliosis [31–33]. Thus, the measurement of cerebellar telomere length should not be complicated by telomerase expression in proliferating glial cells. We found that PBL and cerebellum telomere lengths are correlated in AD patients. However, we were unable to discern a difference in the cerebellar telomere lengths of AD patients compared with control subjects.

2. Methods

2.1. Samples

Cerebellar tissue was obtained from the Center for Neurodegenerative Disease Research Brain Bank at the University of Pennsylvania. Cases (n = 30) were selected from pathologically confirmed AD brains (n = 280), based solely on the availability of matched DNA samples from PBLs that had been collected before death (one PBL DNA sample later proved to be unavailable). Control subjects (n = 22) were selected from normal brains (n = 36), to match most closely the age and gender of the AD cases. The AD patients had an average age at death of 80 years (range, 57–92 years); 73% (n = 22) of patients were female. The mean age at death of control cases was also 80 years (range, 63–98 years); 50% (n = 11) were female. Cerebellar samples from two additional control